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Monographs on drugs which are frequently analyzed in therapeutic drug monitoring

Arzneimittel-Monographien für Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings analysiert werden

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Abstract

In addition to the monographs which have been published recently by the working group "Drug Monitoring" of the Swiss Society of Clinical Chemistry (SSCC) [1–3], new monographs have been written. The aim of these monographs is to provide an overview on the information which is important for the request and interpretation of the results. Therefore, the targeted readers are laboratory health professionals and the receivers of the reports. In this series, several antidepressant and antipsychotic drugs are presented. It is worth noting that the monograph on the antipsychotic clozapine has already been published in 2005 [1]. Information on the indications for therapeutic drug monitoring (TDM), protein binding, metabolic pathways and enzymes involved, elimination half-life time and elimination route(s) of the parent drug and therapeutic or toxic concentrations is provided. Because pre-analytical considerations are of particular importance for therapeutic drug monitoring, information regarding the optimal point in time for the determination of drug concentrations and achievement of steady-state concentrations after changing the dose is given. Furthermore, the stability of the drug and its metabolite(s) after blood sampling is described. For readers with a specific interest, references to important publications are provided. The number of the monographs will be continuously increased. The updated files are presented on the homepage of the SSCC (www.sscc.ch). We hope that these monographs are helpful for the better handling of therapeutic drug monitoring and we are looking forward to comments by the readers.

Keywords: antidepressants; antipsychotics.

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Zusammenfassung

In Ergänzung zu den in den letzten vier Jahren publizierten Arzneimittelmonographien der Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1–3], sind nun weitere Monographien erstellt worden. Ziel dieser Monographien ist es, dem Labormediziner bzw. dem Empfänger der Befunde eine Übersicht über die wichtigsten Informationen zu geben, die für die Veranlassung einer Analyse bzw. für die Interpretation der Resultate hilfreich sind. In dieser Serie werden eine große Zahl von Antidepressiva und Antipsychotika präsentiert. Es muss noch darauf hingewiesen werden, dass die Monographie zu Clozapin, Neuroleptikum, bereits 2005 publiziert worden ist [1]. In den einzelnen Monographien werden klinisch pharmakologische Angaben wie zum Beispiel Indikation für das Therapeutic Drug Monitoring, Proteinbindungen, Metabolisierungswege und daran beteiligte Enzyme, Halbwertzeiten und Eliminationswege der Muttersubstanz, sowie Informationen zu therapeutischen bzw. toxischen Bereichen, zur Verfügung gestellt. Da die Präanalytik gerade beim Therapeutic Drug Monitoring eine wichtige Rolle spielt, werden auch hier Angaben gemacht zu welchem Zeitpunkt eine Bestimmung der Arzneimittelkonzentration sinnvoll ist und wann, nach einer Dosisänderung, der steady-state erreicht ist. Außerdem werden Angaben über die Stabilität der Medikamente bzw. ihrer Metaboliten nach der Blutentnahme gemacht. Für die interessierten Leser sind die verwendeten Referenzen als Zitate aufgeführt. Die Zahl der Monographien wird fortlaufend ergänzt. Die aktuellsten Versionen der Monographien sind auf der Homepage der SGKC abrufbar (www.sscc.ch). Wir hoffen, dass diese Monographien im Umgang mit dem Therapeutic Drug Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Antidepressiva; Antipsychotika.

Amisulpride

General	
• Class of the drug	Antipsychotics
• Synonym(s)	–
• Common trade name(s) in Germany	Solian®
• Conversion factors	μg/L × 2.706 = nmol/L nmol/L × 0.370 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects
• Protein binding	16%
• Elimination half-life	12 h
• Volume of distribution	6 L/kg
• Metabolism	
– Main metabolic pathways	Weakly metabolized (approximately 12% of the dose)
– Active metabolite(s)?	None
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Renal (approximately 70%)
• Typical therapeutic range	100–400 μg/L (270–1080 nmol/L)
• Potentially toxic concentration	Not known [overdose: 10,000 μg/L (27,060 nmol/L), fatality: 42,000 μg/L (113,652 nmol/L)]
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	2–3 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2007. • Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material. 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003. • Service of Pharmacology and Clinical Toxicology, University Hospital of Geneva. http://pharmacoclin.hug-ge.ch/_library/pdf/cytp450.pdf (accession date 27 December 2007). • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Amitriptyline

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Saroten®
• Conversion factors	Amitriptyline: mg/L × 3.61 = μmol/L μmol/L × 0.277 = mg/L Nortriptyline: mg/L × 3.80 = μmol/L μmol/L × 0.263 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	90%–95% (albumin, α1-acid glycoprotein)
• Elimination half-life	17–40 h
• Volume of distribution	6–10 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6, CYP3A, CYP2C19
– Active metabolite(s)?	Nortriptyline, 10-hydroxyamitriptyline and 10-hydroxynortriptyline
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	0.080–0.200 mg/L (0.288–0.722 μmol/L) (amitriptyline + nortriptyline)
• Potentially toxic concentration	> 0.500 mg/L (> 1.80 μmol/L) (amitriptyline + nortriptyline)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	7–10 days
• Time for blood sampling	Before next dose at steady-state or 12–16 h after last dose
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2006. • Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005. • Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Wiesbaden: Abbott Laboratories, Diagnostic Division, 1994. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Aripiprazole

General		
• Class of the drug	Antipsychotics	
• Synonym(s)	–	
• Common trade name(s) in Germany	Abilify®	
• Conversion factors	Aripiprazole:	μg/L × 2.23 = nmol/L
		nmol/L × 0.448 = μg/L
	Dehydroaripiprazole:	μg/L × 2.24 = nmol/L
		nmol/L × 0.446 = μg/L
Clinical pharmacology		
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity	
• Protein binding	99%	
• Elimination half-life	75 h	
• Volume of distribution	5 L/kg	
• Metabolism		
– Main metabolic pathways	CYP3A4, CYP2D6	
– Active metabolite(s)?	Dehydroaripiprazole	
– Inhibitor or inducer of the cytochrome P450 system?	No	
– Other significant pharmacokinetic interactions	None	
• Elimination of parent drug	Mainly hepatic	
• Typical therapeutic range	Preliminary data: Aripiprazole: 100–300 μg/L (220–670 nmol/L)	
• Potentially toxic concentration	Not known	
Pre-analytics		
• Time to steady-state since beginning of treatment or change of posology	~2 weeks	
• Time for blood sampling	Before next dose at steady-state	
• Type(s) of sample	Serum or plasma	
• Stability	Several days at 4°C	
Remarks	Almost no studies available on TDM of aripiprazole and its main active metabolite dehydroaripiprazole.	
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2006. • Kubo M, Mizooku Y, Hirao Y, Osumi T. Development and validation of an LC-MS/MS method for the quantitative determination of aripiprazole and its main metabolite, OPC-14857, in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2005;822:294–9. • DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. Clin Ther 2004;26:649–66. • Mallikaarjun S, Salazar DE, Bramer SL. Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. J Clin Pharmacol 2004;44:197–87. • Product information, BMS. • Kirschbaum KM, Müller MJ, Zernig G, Saria A, Moascher A, et al. Therapeutic drug monitoring of aripiprazole by HPLC with column-switching and spectrophotometric detection. Clin Chem 2005;51:1718–21.	

Clomipramine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Anafranil®
• Conversion factors	mg/L × 3.18 = μmol/L μmol/L × 0.315 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	90–98% (albumin, α1-glycoprotein)
• Elimination half-life	Clomipramine: 19–37 h N-Desmethylclomipramine: 54–77 h
• Volume of distribution	12–17 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6, CYP3A4, CYP1A2
– Active metabolite(s)?	N-Desmethylclomipramine
– Inhibitor or inductor of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	Clomipramine + N-Desmethylclomipramine: 0.175–0.450 mg/L (0.557–1.43 μmol/L)
• Potentially toxic concentration	> 0.450 mg/L (> 1.272 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	7–14 days
• Time for blood sampling	Before next dose at steady-state or 12–16 h after last dose
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005. • Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Abbott Laboratories, Diagnostic Division, 1994. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Duloxetine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Yentreve®
• Conversion factors	μg/L × 3.37 = nmol/L nmol/L × 0.297 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	> 90%
• Elimination half-life	8–17 h
• Volume of distribution	23 L/kg
• Metabolism	
– Main metabolic pathways	CYP1A2 and CYP2D6
– Active metabolite(s)?	None
– Inhibitor or inductor of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions	Not known
• Elimination of parent drug	Hepatic
• Typical therapeutic range	15–150 μg/L (50–500 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~3 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2007. • Anderson D, Reed S, Lintemoot J, Kegler S, De Quintana S, Sandberg M, et al. A first look at duloxetine (Cymbalta) in a postmortem laboratory. J Anal Toxicol 2006;30:576–80. • Satonin DK, McCulloch JD, Kuo F, Knadler MP. Development and validation of a liquid chromatography-tandem mass spectrometric method for the determination of the major metabolites of duloxetine in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2007;852:582–9. • Mercolini L, Mandrioli R, Cazzolla R, Amore M, Raggi MA. HPLC analysis of the novel antidepressant duloxetine in human plasma after an original solid phase extraction procedure. J Chromatogr B Analyt Technol Biomed Life Sci 2007;856:81–7.

Fluvoxamine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Fevarin®
• Conversion factors	μg/L × 3.141 = nmol/L nmol/L × 0.318 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects
• Protein binding	80% (mainly to albumin)
• Elimination half-life	17–22 h
• Volume of distribution	25 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6 (major)
– Active metabolite(s)?	None
– Inhibitor or inducer of the cytochrome P450 system?	Strong inhibition: CYP1A2, CYP2C19 Moderate inhibition: CYP2C9, CYP2D6, CYP3A4/5
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Hepatic
• Typical therapeutic range	150–300 μg/L (470–940 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	4 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2007. • Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material, 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003. • Service of Pharmacology and Clinical Toxicology, University Hospital of Geneva. http://pharmacoclin.hug-ge.ch/_library/pdf/cytp450.pdf (accession date 27 December 2007). • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Haloperidol

General	
• Class of the drug	Neuroleptics
• Synonym(s)	–
• Common trade name(s) in Germany	Haldol®, Haldol® decanoat
• Conversion factors	μg/L × 2.66 = nmol/L nmol/L × 0.38 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	92%
• Elimination half-life	24 h (12–38 h)
• Volume of distribution	7.9 ± 2.5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4, CYP2D6 and reduction
– Active metabolite(s)?	None
– Inhibitor or inducer of the cytochrome P450 system?	Reduced haloperidol (metabolite; inhibits CYP2D6)
– Other significant pharmacokinetic interactions	No
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	5.0–17.0 μg/L (13.0–45.2 nmol/L)
• Potentially toxic concentration	49.4 μg/L (> 130 nmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	One week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Llerena A, Alm C, Dahl ML, Ekqvist B, Bertilsson L. Haloperidol disposition is dependent on debrisoquine hydroxylation phenotype. Ther Drug Monit 1992;14:92–7. • Pan L, Rosseel MT, Belpaire FM. Comparison of two high-performance liquid chromatographic methods for monitoring plasma concentrations of haloperidol and reduced haloperidol. Ther Drug Monit 1998;20:224–30. • Angelo HR, Petersen A. Therapeutic drug monitoring of haloperidol, perphenazine, and zuclopenthixol in serum by a fully automated sequential solid phase extraction followed by high-performance liquid chromatography. Ther Drug Monit 2001;23:157–62. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Imipramine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Tofranil®
• Conversion factors	mg/L × 3.57 = μmol/L μmol/L × 0.280 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	63–96%
• Elimination half-life	6–28 h (11–37 h)
• Volume of distribution	16–20 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6, CYP3A4, CYP2C19, CYP1A2
– Active metabolite(s)?	2-OH-imipramine, desipramine, 2-OH-desipramine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination	Mainly hepatic
• Typical therapeutic range	Imipramine + Desipramine: 0.15–0.25 mg/L (0.54–0.89 μmol/L)
• Potentially toxic concentration	> 1.0 mg/L (> 3.57 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	2–5 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005. • Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Abbott Laboratories, Diagnostic Division, 1994. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Levomepromazine

General	
• Class of the drug	Antipsychotics
• Synonym(s)	Methotrimeprazine
• Common trade name(s) in Germany	Neurocil®
• Conversion factors	μg/L × 3.05 = nmol/L nmol/L × 0.328 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	99%
• Elimination half-life	15–30 h
• Volume of distribution	30 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	None
– Inhibitor or inductor of the cytochrome P450 system?	Inhibition of CYP2D6
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	15–60 μg/L (46–183 nmol/L)
• Potentially toxic concentration	> 3660 μg/L (> 1200 nmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2007. • Brown G, Scott W, Walker S. Sedation in the intensive care unit. Can J Hosp Pharm 1996;49:279–80. • Stahl S. Selecting an atypical antipsychotic by combined clinical experience with guidelines from clinical trials. J Clin Psychiatry 1990;60:31–41. • Canales PL, Olsen J, Miller AL, Crismon ML. Role of antipsychotic polypharmacotherapy in the treatment of schizophrenia. CNS Drugs 1999;12:179–88. • Loennechen T, Dahl SG. High-performance liquid chromatography of levomepromazine (methotrimeprazine) and its main metabolites. J Chromatogr 1990;503:205–15. • Josefsson M, Kronstrand R, Andersson J, Roman M. Evaluation of electrospray ionization liquid chromatography-tandem mass spectrometry for rational determination of a number of neuroleptics and their major metabolites in human body fluids and tissues. J Chromatogr B Analyt Technol Biomed Life Sci 2003;789:151–67.

Lithium

General	
• Class of the drug	Antidepressant
• Synonym(s)	–
• Common trade name(s) in Germany	Quilonorm®: lithium carbonate Togal CLASSIC®: lithium citrate
• Conversion factors	mmol/L × 6.94 = mg/L mg/L × 0.144 = mmol/L
Clinical pharmacology	
• Indications for TDM	Mandatory for individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	0%
• Elimination half-life	15–30 h
• Volume of distribution	0.7–0.9 L/kg
• Metabolism	
– Main metabolic pathways	No metabolism
– Active metabolite(s)?	None
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	Numerous interactions with anti-inflammatory non-steroidal drugs, ACE inhibitors, various diuretics, …
• Elimination of parent drug	Renal > 95%
• Typical therapeutic range	0.5–1.2 mmol/L
• Potentially toxic concentration	> 1.5 mmol/L
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	5–7 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum
• Stability	4 days at 4°C For longer conservation, freeze at –20°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (15. Auflage). Basel: Documed, 2001. • Magnin J-L. Lithium: médicament et outil diagnostic. Labolife 1997; 2:21.

Maprotiline

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Ludiomil®
• Conversion factors	μg/L × 3.61 = nmol/L nmol/L × 0.277 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	90%
• Elimination half-life	43–45 h
• Volume of distribution	23–27 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	Desmethylmaprotiline
– Inhibitor or inducer of the cytochrome P450 system?	Not known
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	125–200 μg/L (451–720 nmol/L)
• Potentially toxic concentration	> 554 μg/L (> 2000 nmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~ 8 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2007. • Kuss HJ, Sirch S, Zhao DY. Assay for maprotiline in human serum with improved sensitivity and selectivity. J Chromatogr B Biomed Appl 1994;656:245–9. • König F, Wolfersdorf M, Löble M, Hauger B. Trimipramine and maprotiline plasma levels during combined treatment with moclobemide in therapy-resistant depression. Pharmacopsychiatry 1997;30:154–7. • Aymard G, Livi P, Pham YT, Diquet B. Sensitive and rapid method for the simultaneous quantification of five antidepressants with their respective metabolites in plasma using high-performance liquid chromatography with diode-array detection. J Chromatogr B Biomed Sci Appl 1997;700:183–9. • Firkusny L, Gleiter CH. Maprotiline metabolism appears to co-segregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. Br J Clin Pharmacol 1994;37:383–8.

Mianserin

General		
• Class of the drug	Antidepressants	
• Synonym(s)	–	
• Common trade name(s) in Germany	Tolvin®	
• Conversion factors	Mianserin:	μg/L × 3.78 = nmol/L
		nmol/L × 0.26 = μg/L
	Desmethylmianserin:	μg/L × 3.99 = nmol/L
		nmol/L × 0.25 = μg/L
Clinical pharmacology		
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity	
• Protein binding	90%	
• Elimination half-life	Mianserin: 15–22 h Desmethylmianserin: 5–21 h	
• Volume of distribution	13 L/kg	
• Metabolism		
– Main metabolic pathways	CYP1A2, CYP2D6	
– Active metabolite(s)?	Desmethylmianserin	
– Inhibitor or inducer of the cytochrome P450 system?	No	
– Other significant pharmacokinetic interactions	None	
• Elimination of parent drug	Mainly hepatic	
• Typical therapeutic range	Mianserin: 15–70 μg/L (57–265 nmol/L)	
• Potentially toxic concentration	> 500 μg/L (> 1900 nmol/L)	
Pre-analytics		
• Time to steady-state since beginning of treatment or change of posology	~ 5 days	
• Time for blood sampling	Before next dose at steady-state	
• Type(s) of sample	Serum or plasma	
• Stability	1 week at 4°C	
Remarks	Chiral drug: enantiomers differ by their metabolism and pharmacology	
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65. • Eap CB, Yasui N, Kaneko S, Baumann P, Powell K. Otani K. Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. Ther Drug Monit 1999;21:166–70.	

Mirtazapine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Remergil®
• Conversion factors	Mirtazapine: μg/L × 3.77 = nmol/L nmol/L × 0.26 = μg/L Desmethylmirtazapine: μg/L × 3.97 = nmol/L nmol/L × 0.25 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	85%
• Elimination half-life	20–40 h
• Volume of distribution	4.5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4, CY2PD6
– Active metabolite(s)?	Desmethylmirtazapine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	No
• Elimination of parent drug	Hepatic 80% Renal <20%
• Typical therapeutic range	Mirtazapine: 40–80 μg/L (150–300 nmol/L) Desmethylmirtazapine: 5.0–20.0 μg/L (20–80 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	• Chiral drug • Enantiomers differ by their metabolism and pharmacology
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Delbressine LP, Moonen ME, Kaspersen FM, Wagenaars GN, Jacobs PL, Timmer CJ, et al. Pharmacokinetics and biotransformation of mirtazapine in human volunteers. Clin Drug Invest 1998;15:45–55. • Pistos C, Koutsopoulou M, Panderi I. A validated liquid chromatographic tandem mass spectrometric method for the determination of mirtazapine and desmethylmirtazapine in human plasma: application to a pharmacokinetic study. Anal Chim Acta 2004:514:15–26. • Shams M, Hiemke C, Härtter S. Therapeutic drug monitoring of the antidepressant mirtazapine and its N-demethylated metabolite in human serum. Ther Drug Monit 2004;26:78–84. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Nortriptyline

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Nortrilen®
• Conversion factors	mg/L × 3.80 = μmol/L μmol/L × 0.263 = mg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	87–93%
• Elimination half-life	18–56 h
• Volume of distribution	20–57 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	10-hydroxynortriptyline
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	0.070–0.170 mg/L (0.266–0.646 μmol/L)
• Potentially toxic concentration	> 0.500 mg/L (> 1.805 μmol/L)
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	4–20 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Baselt RC. Disposition of toxic drugs and chemicals in men, 7th ed. Foster City, CA: Biomedical Publications, 2004. • Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005. • Evans WE, Oellerich M, Holt DW. Therapeutic drug monitoring: clinical guide, 2nd ed. Abbott Laboratories, Diagnostic Division, 1994. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Paroxetine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Seroxat®, Tagonis®
• Conversion factors	μg/L × 3.03 = nmol/L nmol/L × 0.33 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	95%
• Elimination half-life	24 h (6–71 h)
• Volume of distribution	17 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	None
– Inhibitor or inducer of the cytochrome P450 system?	Inhibitor of CYP2D6
– Other significant pharmacokinetic interactions	Not known
• Elimination of parent drug	Hepatic 36% Renal 64%
• Typical therapeutic range	70–120 μg/L (200–365 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2006. • Foglia JP, Sorisio D, Kirshner M, Pollock BG. Quantitative determination of paroxetine in plasma by high-performance liquid chromatography and ultraviolet detection. J Chromatogr B Biomed Sci Appl 1997;693:147–51. • Linder MW, Keck PE Jr. Standards of laboratory practice: antidepressant drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1073–84. • Lucca A, Gentilini G, Lopez-Silva S, Soldarini A. Simultaneous determination of human plasma levels of four selective serotonin reuptake inhibitors by high-performance liquid chromatography. Ther Drug Monit 2000;22:271–6. • Montgomery SA. Efficacy in long-term treatment of depression. J Clin Psychiatry 1996;57(Suppl 2):24–30. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Quetiapine

General	
• Class of the drug	Antipsychotics
• Synonym(s)	–
• Common trade name(s) in Germany	Seroquel®
• Conversion factors	μg/L × 2.607 = nmol/L nmol/L × 0.38 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	83%
• Elimination half-life	5–7 h
• Volume of distribution	7–10 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4 (quetiapine sulfoxide formation)
– Active metabolite(s)?	Clinically not relevant
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	70–170 μg/L (182–443 nmol/L)
• Potentially toxic concentration	Not known [fatality: 18,000 μg/L (47,000 nmol/L)]
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	2–3 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	Quetiapine plasma concentrations show a wide interindividual variation
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2006. • De Vane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clin Pharmacokinet 2001;40:509–22. • Hasselstrom J, Linnet K. Quetiapine serum concentrations in psychiatric patients: the influence of comedication. Ther Drug Monit 2004;26:486–91. • Fernandes PP, Marcil WA. Death associated with quetiapine overdose. Am J Psychiatr 2002;159:2114. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Risperidone

General	
• Class of the drug	Antipsychotics
• Synonym(s)	–
• Common trade name(s) in Germany	Risperdal®, Risperdal Consta®
• Conversion factors	Risperidone: μg/L × 2.436 = nmol/L nmol/L × 0.411 = μg/L 9-OH-risperidone: μg/L × 2.345 = nmol/L nmol/L × 0.426 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	90% (risperidone), 77% (9-OH-risperidone)
• Elimination half-life	Risperidone: 3–4 h 9-OH-risperidone: 15–25 h
• Volume of distribution	1 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	9-OH-risperidone
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	CYP2D6 inhibitors increase risperidone, with a non-fully compensating decrease of 9-OH-risperidone
• Elimination of parent drug	Mainly hepatic (active metabolite mainly renal)
• Typical therapeutic range	Risperidone + 9-OH-risperidone (= "active moiety"): 20–60 μg/L (49–146 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~3–5 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	With long acting (depot) risperidone, steady-state conditions are only reached after 4 injections every 2 weeks (8 weeks after 1st injection). Apparent half-life of "active moiety", after administration of long acting risperidone: 3–6 days The active metabolite 9-OH-risperidon undergoes renal elimination
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2006. • Grant S, Fitton A. Risperidone. A review of its pharmacology and therapeutic potential in the treatment of schizophrenia. Drugs 1994;48:253–73. • Marder SR, Conley R, Ereshefsky L, Kane JM, Turner MS. Clinical guidelines: dosing and switching strategies for long-acting risperidone. J Clin Psychiatry 2003;64:41–6. • Harrison TS, Goa KL. Long-acting risperidone: a review of its use in schizophrenia. CNS Drugs 2004;18:113–32. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65. • Wilson WH. A visual guide to expected blood levels of long-acting injectable risperidone in clinical practice. J Psychiatr Pract 2004;10:393–401.

Sertraline

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Gladem®, Zoloft®
• Conversion factors	μg/L × 3.26 = nmol/L nmol/L × 0.31 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	98%
• Elimination half-life	22–36 h for sertraline 62–104 h for N-Desmethylsertraline
• Volume of distribution	> 20 L/kg
• Metabolism	
– Main metabolic pathways	CYP2B6
– Active metabolite(s)?	N-Desmethylsertraline
– Inhibitor or inducer of the cytochrome P450 system?	Weak inhibitor of CYP2D6 and CYP3A4
– Other significant pharmacokinetic interactions	No
• Elimination of parent drug	Hepatic 50% Renal 50%
• Typical therapeutic range	10–50 μg/L (33–163 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2005. • Linder MW, Keck PE Jr. Standards of laboratory practice: antidepressant drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1073–84. • Lucca A, Gentilini G, Lopez-Silva S, Soldarini A. Simultaneous determination of human plasma levels of four selective serotonin reuptake inhibitors by high-performance liquid chromatography. Ther Drug Monit 2000;22:271–6. • Montgomery SA. Efficacy in long-term treatment of depression. J Clin Psychiatry 1996;57(Suppl 2):24–30. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Trazodone

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Thombran®
• Conversion factors	μg/L × 0.027 = μmol/L μmol/L × 372 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects
• Protein binding	90%
• Elimination half-life	4–7 h
• Volume of distribution	Unknown
• Metabolism	
– Main metabolic pathways	CYP3A4
– Active metabolite(s)?	m-chlorophenyl-piperazine or mCPP (minor)
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	Reported cases of increased levels of digoxin and phenytoin
• Elimination of parent drug	Hepatic
• Typical therapeutic range	650–1500 μg/L (1.75–4.03 μmol/L)
• Potentially toxic concentration	Not known [fatalities: 9000–33,000 μg/L (243–891 μmol/L)]
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	2–3 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2007. • Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material, 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003. • Service of Pharmacology and Clinical Toxicology, University Hospital of Geneva. http://pharmacoclin.hug-ge.ch/_library/pdf/cytp450.pdf (accession date 27 December 2007). • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

Trimipramine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Stangyl®
• Conversion factors	μg/L × 0.00397 = μmol/L μmol/L × 294 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, suspicion of toxicity, side effects
• Protein binding	94%
• Elimination half-life	16–40 h (mean 24 h)
• Volume of distribution	20–50 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	N-desmethyltrimipramine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Hepatic
• Typical therapeutic range	150–350 μg/L (0.51–1.19 μmol/L)
• Potentially toxic concentration	> 1000 μg/L (> 3.4 μmol/L) [fatalities: 9000–12,000 μg/L (30.6–47.6 μmol/L)]
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	4–7 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C
Remarks	None
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2007. • Moffat AC, Osselton D, Widdop B, editors. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and post-mortem material, 3rd ed. London/Chicago, IL: Pharmaceutical Press, 2003. • Service of Pharmacology and Clinical Toxicology, University Hospital of Geneva. http://pharmacoclin.hug-ge.ch/_library/pdf/cytp450.pdf (accession date 27 December 2007). • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65

Venlafaxine

General	
• Class of the drug	Antidepressants
• Synonym(s)	–
• Common trade name(s) in Germany	Trevilor®
• Conversion factors	Venlafaxine: μg/L × 3.605 = nmol/L nmol/L × 0.277 = μg/L O-desmethylvenlafaxine: μg/L × 3.797 = nmol/L nmol/L × 0.263 = μg/L
Clinical pharmacology	
• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	30% (venlafaxine)
• Elimination half-life	4 h (venlafaxine), 10 h (O-desmethylvenlafaxine)
• Volume of distribution	7 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6
– Active metabolite(s)?	Mainly O-desmethylvenlafaxine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	Venlafaxine + O-desmethylvenlafaxine: 195–400 μg/L (721–1480 nmol/L)
• Potentially toxic concentration	Not known
Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology	2–3 days
• Time for blood sampling	Before next dose at steady-state
• Type(s) of sample	Serum or plasma
• Stability:	1 week at 4°C
Remarks	Chiral drug: enantiomers of the parent compound and the active metabolite differ by their metabolism and pharmacology. The extended release (ER) form is preferentially used. The active metabolite O-desmethylvenlafaxine undergoes renal elimination.
References	• Arzneimittelkompendium Schweiz. Basel: Documed, 2006. • Holliday SM, Benfield P. Venlafaxine. A review of its pharmacology and therapeutic potential in depression. Drugs 1995;49:280–94. • Eap CB, Lessard, E, Baumann P, Brawand-Amey M, Yessine MA, O'Hara G, Turgeon J. Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. Pharmacogenetics 2003;13:39–47. • Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry 2004;37:246–65.

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3. Rentsch K, Eap CB, Fathi M, Grignaschi N, Magnin JL, Thormann W, et al. Monograph on drugs which are frequently analyzed in therapeutic drug monitoring. J Lab Med 2008;32:372–81.